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MARSCHER EXAMINER

ART UNIT PAPER NUMBER

1807

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DATE MAILED: 07/11/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on 4-7-95 This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6. _____

Part II SUMMARY OF ACTION

1. Claims 44, 46, 47, and 60-62 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. Claims 1-43, 45, and 48-59 have been cancelled.

3. Claims _____ are allowed.

4. Claims 44, 46, 47, and 60-62 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).

12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

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EXAMINER'S ACTION

Applicants' arguments, filed 4/7/95, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

The amendments to the instant claims that are directed to "body sample" practice contain NEW MATTER because they are not also accompanied by detection of increased expression by antibodies as defined by originally filed claim 5. It is noted that both original claim 8, as filed, and present claim 60 combine body sample detection practice with the performance of this detection via said antibodies. The lack of this antibody detection limitation along with said "body sample" practice results in the rejected claims being broader in scope than the written basis for such body sample detection practice as filed. This broader scope is NEW MATTER in that expression is inclusive

of nucleic acid detection as well as detection practice such as that performed via binding of ligands to a receptor etc. Thus this rejection is based on a lack of a written description of this broader "body sample" detection practice.

Claims 44, 46, 47, 61, and 62 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 44, 46, 47, and 60-62 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to specific hybridization probes such as the insert in pMAC117 or the segment between Nco I and Acc I as cited on page 18, lines 12-26. No antibody probes are enabled. The reason for this rejection is the lack of instantly enabled epidermal growth factor (EGF) receptor protein. The MAC117 protein are instantly described as distinct from the EGF receptor protein at several citations such as that at the bottom of page 19, last 4 lines. On the other hand the close similarity between MAC117 protein and EGF receptor protein sequence is discussed on page 20, lines 12-26. This close similarity is disclosed on page 20, lines 12-26, to include segments of each with 69 % nucleotide sequence identity and 85 % amino acid identity. Therefore antibody probes must be prepared so as to distinguish MAC117 sequences and epitopes from very similar EGF receptor embodiments. This can only be accomplished via the use of EGF receptor protein control samples to define those probes that are usable in the instant invention beyond those specifically

instantly disclosed as to preparation. It is noted that this causes the EGF receptor protein to be essential subject matter to be required for broadly defined probes for negative control usage in selecting MAC117 probes that do not also detect EGF receptor embodiments. The instant disclosure does not include EGF receptor protein epitope information for such negative control use. The closest disclosure to this essential material is that given in Figure 3 showing a partial EGF receptor amino acid sequence. There is however, no disclosure either in Figure 3 or the specification as to either how to prepare or procure EGF receptor protein segments or entire molecules for said negative control use. It is noted that a number of printed publications are cited regarding various EGF receptor disclosures. However, reference to these printed publications is insufficient for the disclosure of essential material as discussed above. See the following paragraph regarding the improper incorporation by reference to a printed publication of essential subject matter. This rejection is reiterated and maintained as given in the previous office action, mailed 10/4/94, since there has been no change in the instant description of EGF receptor protein. Applicants argue that page 8 of the specification has been amended to include both nucleic acid sequence information as well as protein sequence information for the EGF receptor. Consideration of the amendments to page 8 reveals that in contrast only a nucleic acid sequence has been therein amended in. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167.

Claims 44, 46, 47, and 60-62 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44, 46, 47, and 60-62 are vague and indefinite in that the metes and bounds of what applicants mean regarding the practice of the phrase "a MAC117 gene" as cited in claim 44, line 3, or "the MAC117 gene" as cited in claim 60, lines 4 and 8, are not clearly defined. That is, what set of characteristics limit what is meant by "a (or the) MAC117 gene"? No clearly defined set has been disclosed. It is noted that abnormal MAC117 genes are observable in some samples. How abnormal is still within the scope of what applicants mean regarding said gene? Do applicants wish to limit said gene via hybridization characteristics? or nucleotide sequence content? or antigenicity? or tumorigenicity? One possible definition is that given in the specification on pages 4 and 9d, lines 2-5 and 10-12, respectively, where the scope of MAC117 gene practice is limited to genes containing the nucleotide sequence shown in Figure 1. This is also unclear for

two reasons. Firstly, do applicants mean the nucleotide sequence of Figure 1 to only be that sequence shown at the bottom of the Figure cited as 424 bases in length or, alternatively, do applicants mean a gene containing at least the insert sequence of λ MAC117 shown at the top of Figure 1 defined by a restriction map but not actually depicted as a detailed nucleotide sequence similar to that at the bottom of the Figure? At the bottom of page 3 the gene is disclosed as related to but distinct from the EGF receptor gene. Is this the basis for defining the gene and if so what distinctness measurement defines the MAC117 metes and bounds versus that of the EGF receptor? Applicants argue firstly that the standard textbook definition of a gene is given in Watson et al. as a DNA sequence that codes for amino acids. This is non-persuasive in clearly and concisely defining a gene because this definition would include whole chromosomes, large subsegments thereof, or a wide variety of coding segments that are unrelated to MAC117. Applicants then go on to argue that the Figure 1 depiction of two exons defines the MAC 117 gene. This is non-persuasive in that applicants also admit therein that only a part of the polypeptide chain of the MAC117 gene product is therein shown. This clearly lacks definition of the metes and bounds of said gene. It is noted that defining a subsection of a nucleic acid fails to define its termini or other subsections. Applicants then go on to discuss the recognition of EcoR I segments of various cell samples with a v-erbB probe. This again is non-persuasive in that only a subsegment is defined thereby.

without defining the metes and bounds of other segments including termini beyond which nucleic acid sequence is no longer deemed MAC117 gene sequence. Applicants then go on to argue that Figures 5A and 5B define the entire coding region of the MAC117 gene. This is also non-persuasive since consideration of Figure 5A and 5B reveals no termini that define the metes and bounds of said gene. It is acknowledged that the MAC117 gene appears to be contained somewhere in the map shown in Figures 5A and 5B. This still does not define concisely where therein. The definition of the metes and bounds of the MAC117 gene is still vague and indefinite for two reasons. One is a lack of concise metes and bounds and the other is a lack of whether applicants actually mean the gene to be the structural gene that encodes the amino acids of MAC117 protein such as a cDNA sequence might.

Applicants have argued by pointing to some evidence for intron and exon definition and also by pointing to coding regions. Does this mean that applicants are not including promoter region(s) into the gene definition? Do applicants mean the gene to be the exact coding region with introns only? Clarification of the metes and bounds of what is meant regarding the claimed MAC117 gene is still requested.

Claim 44 cites the intended method to be directed to "diagnosing or evaluating" in line 1 but only accomplishes in recited steps what is deemed "diagnosing" in line 6 cited therein as "indicating the presence of cancer or a cancer with a more malignant phenotype". It is acknowledged that evaluation might

be construed to be correlated to the extent of amplification or increased expression of a MAC117 gene. That is, minimal amplification or expression could be viewed as a early cancer or one that is in remission whereas large amplification or overexpression could indicate a cancer that is worse than others or becoming more malignant etc. These evaluation criteria which correlates the extent of cancer seriousness to MAC117 amplification or increased expression however are not evident from the claim but only become possible interpretations after contemplating the claim wording at length. Such implied correlations fail to meet the requirements of 35 USC § 112 due to their lack of clarity etc. Clarification of claim wording regarding what evaluation applicants intend to be practiced in claims 44 and those dependent therefrom. This rejection is reiterated and maintained as given in the previous office action, mailed 10/4/94. Applicants argue that the phrase amended into claim 44 directed to a "cancer with a more malignant phenotype" corresponds to the evaluating of line 1 therein. This is non-persuasive since as noted above implied and unclear interpretations of claim wording fail to meet the requirements of 35 U.S.C. § 112, second paragraph. Since claim 44 etc. lacks any statement that defines what is meant regarding "increased" expression, it is not clear from the claim what is meant regarding the "evaluating" practice. That is, one confusing interpretation of claim 44 is that merely the presence of amplification or increased expression over normal samples is

indicative of cancer or a more malignant phenotype whereas after some contemplation of the invention a more malignant phenotype is indicated most likely by comparing two cancer patients wherein one has more amplification or expression than the other thus indicating a more malignant phenotype in the patient with higher amplification or expression. Alternatively, increased amplification or expression in a patient over time could indicate a more malignant phenotype. To expand on the other interpretation a cancer may lack detectable amplification or expression and then show a more malignant phenotype via changing to a state of producing detectable amplification or increased expression. To reiterate a number of possible implied but not clearly set forth interpretations are possible for the practice of claim 44 etc. thus making the metes and bounds of its practice unclear as previously rejected.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 44, 46, and 60 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by either Semba et al. or Yamamoto et al.

Semba et al. discloses the amplification of c-erbB-2 in human adenocarcinoma of the salivary gland in the title,

abstract, and the section on page 6500, entitled "Association of Amplification of the c-erbB-2 Gene with a Primary Human Tumor". These results read on the diagnostic methods as instantly claimed for the carcinomas therein analyzed. Yamamoto et al. disclose c-erbB-2 amplification in cancer cells in the abstract which is cited therein as a suggestion that such amplification is sometimes involved in the neoplastic process. This is a conservative evaluation of diagnostic use of the detection of such amplification based on data for cell samples that serve as the basis for the instant invention also and therefore are equally supportive of diagnostic methods and therefore read on the above rejected claims. Semba et al. and Yamamoto et al. were published less than one year prior to the parent application serial number 06/836,414 thus making a 102(a) rejection appropriate due to priority given to said parent application for the subject matter of the above rejected claims. Applicants argue that the instant invention was conceived and reduced to practice prior to the publication dates of the above listed references and submit an unsigned Declaration under 37 CFR § 1.131 as evidence of this. This is non-persuasive in overcoming the rejection for two reasons. Firstly, an unsigned Declaration is insufficient due to the lack of said signatures. Secondly, consideration of the reveals a lack of a statement that the conception and reduction to practice of the instant invention occurred in the United States as required for such Declarations to be effective in overcoming the rejection as set forth.

Claims 47, 61, and 62 are allowable over the prior art of record because of reasons of record.

No claim is allowed.

Applicants' amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is either (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM
A. MARSCHEL, Ph.D.
July 7, 1995

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